# Summary of the Risk Management Plan for Revestive

Revestive® (Teduglutide)
Marketing Authorisation Holder: Takeda Pharma AG Switzerland
EU RMP Version 9.0
Date: 16 Aug 2019

Disclaimer

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Revestive is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Revestive in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch ) approved and authorized by Swissmedic. Takeda Pharma AG Switzerland is fully responsible for the accuracy and correctness of the content of the published summary RMP of Revestive.

**SUMMARY OF THE RISK MANAGEMENT PLAN**

**Summary of Risk Management Plan for Revestive**

This is a summary of the risk management plan (RMP) for Revestive. The RMP details important risks of Revestive, how these risks can be minimised, and how more information will be obtained about Revestive's risks and uncertainties (missing information).
Revestive's summary of product characteristics (SmPC) and its package information leaflet (PIL) give essential information to healthcare professionals and patients on how Revestive should be used.
This summary of the RMP for Revestive should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).
Important new concerns or changes to the current ones will be included in updates of Revestive's RMP.

## *I. The medicine and what it is used for*

Revestive is authorised for the treatment of patients aged 1 year and above with short bowel syndrome (SBS). Patients should be stable following a period of intestinal adaptation. (see the SmPC for the full indication). Revestive contains teduglutide as the active substance and it is given by subcutaneous injection once daily, alternating sites between 1 of the 4 quadrants of the abdomen. In case the injection into the abdomen is hampered by pain, scarring or hardening of the tissue, the thigh can also be used. Revestive should not be administered intravenously or intramuscularly.
Further information about the evaluation of Revestive benefits can be found in Revestive European Public Assessment Reports (EPAR), including in its plain-language summary, available on the EMA website, under the medicine's webpage:

***https://www.ema.europa.eu/en/medicines/human/EPAR/revestive***

## *II. Risks associated with the medicine and activities to minimise or further characterise the risks*

Important risks of Revestive, together with measures to minimise such risks and the proposed studies for learning more about Revestive' s risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine’s legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Revestive is not yet available, it is listed under ‘missing information’ below.

### *II.A List of important risks and missing information*

Important risks of Revestive are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Revestive. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of Important Risks and Missing Information

| | |
|---|---|
| Important identified risks | Biliary AEs. |
| | Pancreatic AEs. |
| | Cardiovascular AEs associated with fluid overload. |
| | GI stenosis and obstruction. |
| | GI stoma complications. |
| | Intestinal polyps. |
| | Benign neoplasia of the GI tract including the hepatobiliary system. |
| | Tumour promoting ability. |
| | Anxiety. |
| Important potential risks | AEs associated with increased absorption of oral concomitant medications. |
| | Local skin reactions. |
| | Potential for off-label use in patients with active Crohn's disease. |
| | Medication errors. |
| | Compromised nutritional status. |
| Missing information | Lack of experience for administration of teduglutide in subjects with severe, clinically unstable concomitant diseases, e.g. cardiovascular, respiratory, renal, infectious, endocrine, hepatic or CNS, or in patients with malignancies within the last 5 years. |
| | Lack of experience in pregnant or lactating women. |
| | Lack of experience in children aged less than 1 year |
| | Long-term safety in paediatric population. |
| | Limited long-term safety data over 1 year of exposure. |
| | Lack of data in subjects with pre-existing severe hepatic impairment. |
| AE=adverse event; CNS=central nervous system; CRP=C-reactive protein; ECP=E. coli protein; GI=gastrointestinal | |

## *II.B Summary of important risks*

**Table 1. Important Identified Risk – Biliary adverse events**

| | |
|---|---|
| Evidence for linking the risk to the medicine | **Non-clinical**: Teduglutide-induced hyperplasia in the gall bladder and the biliary ducts were observed in nonclinical studies and may theoretically lead to concentration of the bile with increased risk for the occurrence of sludge and stones.<br>**Clinical studies**: Biliary events like cholecystitis, cholangitis, and cholelithiasis have been observed in clinical trials. No obstruction of the bile ducts has been observed in clinical and nonclinical studies with teduglutide. |
| Risk factors and risk groups | The SBS population is too small for stratified data analysis and the existence of risk groups is unknown.<br>Risk factors for cholecystitis mirror those for cholelithiasis. The overall incidence of gallbladder disease was about twice as high in women as in men, and it increased with age in both sexes without any evidence of an excess in the forties. Increase in weight and number of pregnancies were each associated with increased incidence (Friedman, 1966). Additional risk factors include rapid weight loss and pregnancy (elevated progesterone levels during pregnancy may cause biliary stasis). Also, recent operation and consequences of previous intestinal surgery are associated with the occurrence of cholecystitis (Kimura, 2007). |
| Risk minimisation measures | **Routine risk minimisation measures:**<br>SmPC Section 4.2, Section 4.4 and Section 4.8<br>**Additional risk minimisation measures:**<br>No risk minimisation activities. |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities:**<br>Registry TED-R13-002<br>See section II.C of this summary for an overview of the post-authorisation development plan. |

**Table 2. Important Identified Risk – Pancreatic adverse events**

| | |
|---|---|
| Evidence for linking the risk to the medicine | **Non-clinical**: Teduglutide-induced hyperplasia in the gall bladder and the biliary ducts were observed in nonclinical studies and may theoretically lead to concentration of the bile with increased risk for the occurrence of sludge and stones. Also, hyperplasia of the pancreatic duct has been shown in nonclinical studies.<br>**Clinical studies:** Pancreatic adverse events such as chronic and acute pancreatitis, pancreatic duct stenosis, pancreas infection and increased blood amylase and lipase have been reported in clinical studies. |
| Risk factors and risk groups | The SBS population is too small for stratified data analysis and the existence of risk groups is unknown. |

**Table 2. Important Identified Risk – Pancreatic adverse events**

| | |
|---|---|
| | Pancreatitis is generally caused by toxic-metabolic events (e.g., alcohol, smoking, hyperlipidaemia), by duct obstruction and may also have a genetic, idiopathic or autoimmune aetiology (Jupp, 2010). Thus, risk factors for pancreatitis partially mirror those for cholelithiasis and sludge. The overall incidence of gallbladder disease was about twice as high in women as in men, and it increased with age in both sexes without any evidence of an excess in the forties. Increase in weight and number of pregnancies were each associated with increased incidence (Friedman, 1966). Also, the use of PN and the potential hyperlipidaemia might contribute to the occurrence of pancreatitis. |
| Risk minimisation measures | **Routine risk minimisation measures:**<br>SmPC Section 4.2, Section 4.4 and Section 4.8<br>**Additional risk minimisation measures:**<br>No risk minimisation activities. |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities:**<br>Registry TED-R13-002<br>See section II.C of this summary for an overview of the post-authorisation development plan. |

**Table 3. Important Identified Risk: Cardiovascular adverse events associated with fluid overload**

| | |
|---|---|
| Evidence for linking the risk to the medicine | **Clinical Trials**: Fluid overload and congestive heart failure have been observed in adults in clinical trials. |
| Risk factors and risk groups | The SBS population is too small for stratification. |
| Risk minimisation measures | **Routine risk minimisation measures:**<br>SmPC Section 4.2, and Section 4.4<br>**Additional risk minimisation measures:**<br>No risk minimisation activities. |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities:**<br>Registry TED-R13-002<br>See section II.C of this summary for an overview of the post-authorisation development plan. |

**Table 4. Important Identified Risk: Gastrointestinal stenosis and obstruction**

| | |
|---|---|
| Evidence for linking the risk to the medicine | **Clinical Trials**. Cases of intestinal obstruction have been reported in adult clinical studies. |
| Risk factors and risk groups | The SBS population is too small for stratified data analysis. |

**Table 4. Important Identified Risk: Gastrointestinal stenosis and obstruction**

| | |
|---|---|
| Risk minimisation measures | **Routine risk minimisation measures:**<br>SmPC Section 4.2, Section 4.4 and Section 4.8<br>**Additional risk minimisation measures:**<br>No risk minimisation activities. |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities:**<br>Registry TED-R13-002<br>See section II.C of this summary for an overview of the post-authorisation development plan. |

**Table 5. Important Identified Risk: Gastrointestinal stoma complications**

| | |
|---|---|
| Evidence for linking the risk to the medicine | **Clinical Studies**: Stoma complications have been observed in clinical studies. |
| Risk factors and risk groups | The SBS population is too small for stratified data analysis and the existence of risk groups is unknown. |
| Risk minimisation measures | **Routine risk minimisation measures:**<br>SmPC Section 4.2, and Section 4.8<br>**Additional risk minimisation measures:**<br>No risk minimisation activities. |

**Table 6. Important Identified Risk: Intestinal polyps**

| | |
|---|---|
| Evidence for linking the risk to the medicine | **Nonclinical:** Teduglutide bears the potential risk to enhance the growth of colon polyps. In the rat carcinogenicity study, benign tumours were found in the small bowel and the extrahepatic bile ducts.<br>**Clinical:** Polyps were observed in adult patient in clinical studies. |
| Risk factors and risk groups | The SBS population is too small for stratified data analyses and the existence of risk groups is unknown. However, data from literature and from other populations indicate the following risk factors:<br>**Age**<br>Background prevalence between 23 and 41% in persons between ages of 50 and 82 years (Lieberman and Smith 1991; Rex et al. 1991; Johnson et al. 1990; DiSario et al. 1991) and between 7 and 40% for persons younger than 50 years of age (Liljegren et al. 2003).<br>**Crohn's Disease / Ulcerative Colitis** |

**Table 6. Important Identified Risk: Intestinal polyps**

| | |
|---|---|
| | The risk for colorectal cancer for subjects with active Crohn's disease/ulcerative colitis is approximately an 18-fold increase greater than for a person without chronic inflammatory bowel disease (Gillen et al. 1994).<br>**Presence of colon**<br>Within the intestinal tract, colonic neoplasms are most frequent in men. Therefore, SBS subjects with colon may represent a subgroup with increased risk compared with subjects without colon. |
| Risk minimisation measures | **Routine risk minimisation measures:**<br>SmPC Section 4.2, Section 4.3, and Section 4.4<br>**Additional risk minimisation measures:**<br>No risk minimisation activities. |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities:**<br>Registry TED-R13-002<br>See section II.C of this summary for an overview of the post-authorisation development plan. |

**Table 7. Important Identified Risk: Benign neoplasia of the gastrointestinal tract including the hepatobiliary system**

| | |
|---|---|
| Evidence for linking the risk to the medicine | **Nonclinical:** In the rat carcinogenicity study, benign tumours were found in the small bowel and the extrahepatic bile ducts.<br>**Clinical**: These observations were not confirmed in clinical studies of more than one-year duration. |
| Risk factors and risk groups | The SBS population is too small for stratified data analyses and the existence of risk factors or groups is unknown. However, data from literature and from other populations indicate the following risk factors and groups:<br>Populations at risk of small bowel neoplasia include subjects with Crohn's disease, celiac disease, polyposis syndromes, or a history of small bowel-diverting surgeries and subjects elder than 50 years of age (Buckley and Fishman 1998; Lieberman and Smith 1991; Rex et al., 1991; Johnson et al. 1990; DiSario et al. 1991).<br>Based on known risk factors for cholangiocarcinoma, it can be assumed that subjects with chronic inflammation of the biliary ducts or with liver cirrhosis of different origin are at increased risk for the occurrence of cholangiomas (Sorensen et al. 1998). |
| Risk minimisation measures | **Routine risk minimisation measures:**<br>SmPC Section 4.2, Section 4.3, Section 4.4, and Section 5.1.<br>**Additional risk minimisation measures:** |

**Table 7. Important Identified Risk: Benign neoplasia of the gastrointestinal tract including the hepatobiliary system**

| | |
|---|---|
| | No risk minimisation activities. |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities:**<br>Registry TED-R13-002<br>See section II.C of this summary for an overview of the post-authorisation development plan. |

**Table 8. Important Identified Risk: Tumor promoting ability**

| | |
|---|---|
| Evidence for linking the risk to the medicine | **Nonclinical**:<br>Teduglutide was negative when tested in the standard battery of tests for genotoxicity.<br>In a rat carcinogenicity study, treatment related benign neoplasms included tumours of the bile duct epithelium in males exposed to teduglutide plasma levels approximately 32- and 155-fold higher than obtained in patients administered the recommended daily dose (incidence of 1 out of 44 and 4 out of 48, respectively). Adenomas of the jejunal mucosa were observed in 1 out of 50 males and 5 out of 50 males exposed to teduglutide plasma levels approximately 10- and 155-fold higher than obtained in patients administered the recommended daily dose. In addition, a jejunal adenocarcinoma was observed in a male rat administered the lowest dose tested (animal:human plasma exposure margin of approximately 10-fold).<br>**Clinical studies**: The clinical studies conducted could neither exclude nor confirm such an increased risk. |
| Risk factors and risk groups | The SBS population is too small for stratified data analyses and the existence of risk factors or groups is unknown.<br>In general, risk groups are subjects with an increased risk for developing any kind of tumours such as an elderly population.<br>In addition, certain subject characteristics like smoking, immune suppression therapy or previous cancers, which are known to be associated to a higher incidence / prevalence of neoplasias, are considered additional risk factors. |
| Risk minimisation measures | **Routine risk minimisation measures:**<br>SmPC Section 4.2, Section 4.3, Section 4.4, and Section 5.1.<br>**Additional risk minimisation measures:**<br>No risk minimisation activities. |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities:**<br>Registry TED-R13-002 |

**Table 8. Important Identified Risk: Tumor promoting ability**

| | |
|---|---|
| | See section II.C of this summary for an overview of the post-authorisation development plan. |

**Table 9. Important Identified Risk: Anxiety**

| | |
|---|---|
| Evidence for linking the risk to the medicine | In the placebo-controlled studies CL0600-004 and CL0600-020, a higher reporting rate of subjects with anxiety has been observed in the teduglutide group compared with the placebo group. A potential mechanism for this observation is unknown. However, due to the facts that anxiety can have severe consequences and that no reports occurred in the placebo group, anxiety is considered an important identified risk. |
| Risk factors and risk groups | The SBS population is too small for stratified data analysis and the existence of risk groups is unknown. |
| Risk minimisation measures | **Routine risk minimisation measures:**<br>SmPC Section 4.8<br>**Additional risk minimisation measures:**<br>No risk minimisation activities. |

**Table 10. Important Potential Risk: Adverse events associated with increased absorption of oral concomitant medications**

| | |
|---|---|
| Evidence for linking the risk to the medicine | **Clinical Trials:** Based upon the pharmacodynamic effect of teduglutide, there is a potential for increased absorption of concomitant medicinal products. No confirmed event of increased absorption of concomitant medications has occurred in the teduglutide development program. |
| Risk factors and risk groups | The SBS population is too small for stratified data analysis and the existence of risk groups is unknown. |
| Risk minimisation measures | **Routine risk minimisation measures:**<br>SmPC Section 4.4 and Section 4.5.<br>**Additional risk minimisation measures:**<br>No risk minimisation activities. |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities:**<br>Registry TED-R13-002<br>See section II.C of this summary for an overview of the post-authorisation development plan. |

**Table 11. Important Potential Risk: Local skin reactions**

| | |
|---|---|
| Evidence for linking the risk to the medicine | **Non-Clinical**: Treatment-related inflammatory lesions at the injection sites were observed in all preclinical animal species.<br>**Clinical Studies**: Injection site reactions occurred in 26% of SBS patients treated with teduglutide, compared to 5% of patients in the placebo arm. The reactions included injection site haematoma, injection site erythema, injection site pain, injection site swelling and injection site haemorrhage. The majority of reactions were moderate in severity and no occurrences led to drug discontinuation. |
| Risk factors and risk groups | The SBS population is too small for stratified data analysis and the existence of risk groups is unknown. |
| Risk minimisation measures | **Routine risk minimisation measures:**<br>SmPC Section 4.8<br>**Additional risk minimisation measures:**<br>No risk minimisation activities. |

**Table 12. Important Potential Risk: Potential off-label use in patients with active Crohn's disease**

| | |
|---|---|
| Evidence for linking the risk to the medicine | Post marketing reports |
| Risk factors and risk groups | The Risk group might be patients with active Crohn's disease with concomitant SBS not adequately treated for Crohn's disease. |
| Risk minimisation measures | **Routine risk minimisation measures:**<br>SmPC Section 4.1, Section 4.2.<br>**Additional risk minimisation measures:**<br>No risk minimisation activities |

**Table 13. Important Potential Risk: Medication error**

| | |
|---|---|
| Evidence for linking the risk to the medicine | **Clinical Studies and Post Marketing**: Reports of accidental overdose were seen in clinical studies. Reports medication errors are seen during the post-marketing period. |
| Risk factors and risk groups | The SBS population is too small for stratified data analysis and the existence of risk groups is unknown. |
| Risk minimisation measures | **Routine risk minimisation measures:** |

**Table 13. Important Potential Risk: Medication error**

| | |
|---|---|
| | SmPC Section 4.2, Section 4.9 and Section 6.6 |

**Table 14. Important Potential Risk: Compromised nutritional status**

| | |
|---|---|
| Evidence for linking the risk to the medicine | Not applicable |
| Risk factors and risk groups | The SBS population is too small for stratified data analysis and the existence of risk groups is unknown. Overall all patients getting partially or fully independent form PN/IV could be at risk for an imbalance of nutritional status. |
| Risk minimisation measures | **Routine risk minimisation measures:**<br>SmPC Section 4.2<br>**Additional risk minimisation measures:**<br>No risk minimisation activities. |

**Table 15. Missing Information – Lack of experience for administration of teduglutide in subjects with severe, clinically unstable concomitant diseases, e.g. cardiovascular, respiratory, renal, infectious, endocrine, hepatic or CNS, or in patients with malignancies within the last 5 years.**

| | |
|---|---|
| Risk minimisation measures | **Routine risk minimisation measures:**<br>SmPC Section 4.4<br>**Additional risk minimisation measures:**<br>No risk minimisation activities. |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities:**<br>Registry TED-R13-002<br>See section II.C of this summary for an overview of the post-authorisation development plan. |

**Table 16. Missing Information – Lack of experience in pregnant or lactating women.**

| | |
|---|---|
| Risk minimisation measures | **Routine risk minimisation measures:**<br>SmPC Section 4.6<br>**Additional risk minimisation measures:**<br>No risk minimisation activities. |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities:**<br>Registry TED-R13-002 |

**Table 16. Missing Information – Lack of experience in pregnant or lactating women.**

| | |
|---|---|
| | See section II.C of this summary for an overview of the post-authorisation development plan. |

**Table 17. Missing Information - Lack of experience in the children less than 1 year**

| | |
|---|---|
| Risk minimisation measures | **Routine risk minimisation measures:**<br>SmPC 4.2 and Section 4.8<br>**Additional risk minimisation measures:**<br>No risk minimisation activities. |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities:**<br>Registry TED-R13-002<br>See section II.C of this summary for an overview of the post-authorisation development plan. |

**Table 18. Missing Information – Long-term safety in the paediatric population.**

| | |
|---|---|
| Risk minimisation measures | **Routine risk minimisation measures:**<br>SmPC Section 4.2 and Section 4.8<br>**Additional risk minimisation measures:**<br>No risk minimisation activities. |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities:**<br>Registry TED-R13-002<br>See section II.C of this summary for an overview of the post-authorisation development plan. |

**Table 19. Missing Information – Limited long-term safety data over 1 year of exposure.**

| | |
|---|---|
| Risk minimisation measures | No risk minimisation activities are proposed at this time. Additional safety data will be available following completion of the NIS. |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities:**<br>Registry TED-R13-002<br>See section II.C of this summary for an overview of the post-authorisation development plan. |

**Table 20. Missing Information - Lack of data in subjects with pre-existing severe hepatic impairment.**

| | |
|---|---|
| Risk minimisation measures | **Routine risk minimisation measures:**<br>SmPC Section 4.2<br>**Additional risk minimisation measures:**<br>No risk minimisation activities. |
| Additional pharmacovigilance activities | **Additional pharmacovigilance activities:**<br>Registry TED-R13-002<br>See section II.C of this summary for an overview of the post-authorisation development plan. |

## *II.C Post-authorisation development plan*

### II.C.1 Studies which are conditions of the marketing authorization

The following studies are conditions of the marketing authorisation:

**Table 21. Studies Which are Conditions of the Marketing Authorisation**

| Study name | Purpose of the study |
|---|---|
| Registry TED-R13-002: A Prospective, Multi-centre Registry for Patients with Short Bowel Syndrome | Primary objective: To evaluate the long-term safety profile for patients (adults and children) with SBS who are treated with teduglutide in a routine clinical setting.<br>Secondary objective: To evaluate long-term clinical outcome in subjects with SBS. |

### II.C.2 Other studies in the post-authorisation development plan

There are no studies required for Revestive.